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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,777	07/19/2004	John Robert Birch	BJS-4145-14	5040

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EXAMINER	
MCGILLEM, LAURA L	
ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,777	BIRCH ET AL.	
	Examiner	Art Unit	
	Laura McGillem	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 3-7, 10-11, 14-15, 17-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,10,11,14,15 and 17-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

It is noted that claims 1 and 7 have been amended, claims 2, 8-9, 12-13 and 16 have been cancelled and claims 25-27 have been added in the response filed 4/30/2007. Claims 1, 3-7, 10-11, 14-15 and 17-27 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-15, 17-18, and 21-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14 and 23 are dependent claims that recite the limitations "process of claim 13" or "process according to claim 13". Claim 13 has been cancelled, so it is not clear to what process the Applicants intend that the limitations of claims 14 and 23 should apply, since there are other claims directed to a process. There is insufficient antecedent basis for this limitation in the claims.

Claims 17 and 21 are dependent claims that recite the limitation "cell of claim 16". Claim 16 has been cancelled so it is not clear to what cell the Applicants intend that the limitations of claims 17 and 21 should apply since there are other claims directed to a cell. There is insufficient antecedent basis for this limitation in the claims.

Claims 15, 18, 22 and 24 are indefinite insofar as they are dependent on indefinite claims.

Double Patenting

Applicant is advised that should claims 19-20 be found allowable, claims 25-26 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Applicant's arguments filed 4/30/2007 have been fully considered and are persuasive. The rejection of claims 1, 3-7, 10-11, 19-24 under 35 U.S.C. 103(a) as being patentable over WO 99/05267 (Brandt et al) in view of Pu et al (Mol. Biotechnol.1998. Vol. 10, pp.17-25) has been withdrawn. Claims 8, 12-13 and 16 have been cancelled

The rejection of claims 1, 3-7, 10-11, 16, 19-24 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,395,484 (Brandt et al, 5/28/2002) in view of Pu et al (Mol. Biotechnol.1998. Vol. 10, pp.17-25) has been withdrawn. Claims 8, 12-13 and 16 have been cancelled.

The rejection of claims 1, 7, 14-15 and 17-18 under 35 U.S.C. 103(a) as being unpatentable over WO 99/05267 (Brandt et al) in view of Pu et al (Mol. Biotechnol.1998. Vol. 10, pp.17-25) and further in view of Hermentin et al (U.S. Patent No. 6,096,555) has been withdrawn. Claims 8, 12-13 and 16 have been cancelled.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-7, 10-11, 19-20 and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bebbington et al (U.S. Patent No. 5,891,693, 4/6/1999) as evidenced by Barsomian et al (U.S. Patent No, 5,238,821, 8/24/1993) in view of Brandt et al (U.S. Patent No. 6,395,484, of record). This is a NEW rejection.

Applicants claim a glutamine-auxotropic human cell transfected with (a) an exogenous DNA sequence encoding a sialylated protein or an exogenous DNA sequence capable of altering the expression of an endogenous gene encoding a sialylated protein, and which exogenous DNA sequence further comprises a selectable marker selected from the group consisting of DHFR, adenosine deaminase, asparagine synthetase, aspartate transcarbamylase, metallotionein-1, ornithine decarboxylase, P-glycoprotein, ribonucleotide reductase, thymidine kinase and xanthine-guanine phosporibosyl transferase, and (b) an exogenous DNA sequence encoding a glutamine

synthetase as a selectable marker, wherein these exogenous DNA sequences are located on more than one DNA construct, wherein said DNA construct is a vector, and wherein said transfected cell is capable of producing said protein and is capable of growing in a glutamine-free and serum-free medium.

Bebbington et al teach mouse and rat lymphoid cell lines that can be transformed to glutamine independence by incorporating a gene encoding glutamine synthetase (GS) so that the cells can grow in glutamine-free medium. Bebbington et al teach that the cell preferably contains a gene coding for a heterologous protein in which the gene is encoded on a separate vector (see column 2, lines 8-20, 25-30 and 44-51, for example), which meets the limitation of exogenous DNA sequences being located on more than one DNA construct. Bebbington et al teach examples of heterologous proteins as human growth hormone, or tPA or tissue inhibitor of metalloproteinase (see column 2, lines 31-36, for example). Barsomian et al disclose that tPA is a sialylated glycoprotein (see column 2, lines 49-52, for example). Bebbington et al teach that the expression of the heterologous protein is substantially increased by selection for GS gene amplification (see column 2, lines 52-55, for example), which meets the limitation of GS as a selection marker.

Bebbington et al do not teach a human glutamine-auxotrophic cell. Bebbington et al do not teach an exogenous sequence encoding a sialylated protein that further comprises a selectable marker such as claimed. Bebbington et al do not teach growing the cells in serum-free medium.

Brandt et al teach human cells (HT1080) for the preparation of human proteins in order to produce human proteins in economical yields in a form that is suitable for production of a pharmaceutical preparation (see column 1, lines 12-17, for example) which meets the limitation of glutamine-auxotropic human cell line or an immortalized fibrosarcoma HT1080 cell line. Brandt et al teach the advantage of using **serum free culture medium** for culture of human cells because purification of proteins from serum free culture is substantially easier and has no danger of contamination with animal pathogens (see column 2, lines 22-34, for example) which meets the limitation of a human cell growing in a serum free culture. Brandt et al teach that it is advantageous to use a human cell line that synthesizes a desired protein with a glycosylation protein, especially a sialic acid protein comparable to that of the naturally occurring target protein (see column 3, lines (19030, for example).

Brandt et al also teach that a negative or positive selection marker or amplification gene can be included and can be DHFR, adenosine deaminase, ornithine decarboxylase or a thymidine kinase gene (see column 4, lines 56-65, for example), which meets the limitation of a gene further comprising a selectable marker selected from the group consisting of DHFR, adenosine deaminase, asparagine synthetase, aspartate transcarbamylase, metallotionein-1, ornithine decarboxylase, P-glycoprotein, ribonucleotide reductase, thymidine kinase and xanthine-guanine phosporibosyl transferase.

It would have been obvious to the skilled artisan at the time the invention was made to modify the teaching of Bebbington et al from making and using a rodent

glutamine auxotrophic cell to produce an exogenous sialylated protein such as tPA to a human cell as taught by Brandt et al to produce a human exogenous sialylated protein because Brandt et al disclose that human cells are preferred for the preparation of human proteins in order to produce human proteins in economical yields in a form that is suitable for production of a pharmaceutical preparation. The motivation to use a human glutamine auxotrophic cell that is transfected with a glutamine synthetase sequence and a separate vector comprising a sequence for an exogenous sialylated protein is the expected benefit of being able to synthesize a target protein with a sialic acid moiety glycosylation pattern that is comparable to that of the naturally occurring target protein (see column 3, lines 23-30, for example).

It also would have been obvious to the skilled artisan at the time the invention was made to modify the teaching of Bebbington et al from making and using a glutamine auxotrophic cell that is capable of growing in serum-free medium because Brandt teach the importance of serum-free medium for cultivation. The motivation to use a serum-free medium is the expected benefit of being able to reduce the danger of contamination of the protein produced with animal pathogens that might be introduced by using animal serum (see column 2, lines 22-35, for example).

It also would have been obvious to the skilled artisan at the time the invention was made to modify the teaching of Bebbington et al and use a second exogenous DNA sequence as a selection marker and amplification gene because Brandt et al teaches clone selection and gene amplification using a positive or negative selection marker. The motivation to use a selection marker and amplification gene such as DHFR is the

expected benefit as disclosed by Brandt et al of being able to use a gene with a sensitivity for a selection agent in order to increase the expression of an gene to be produced by culturing the cell in the presence of increasing concentrations of a selection agent (i.e. methotrexate) (see column 10, lines 36-44, for example). There is a reasonable expectation of success to make and use a human glutamine auxotrophic cell wherein these exogenous DNA sequences are located on more than one DNA vector construct, because it has worked previously in the references cited.

Therefore Bebbington et al as evidenced by Barsomian et al in view of Brandt et al render obvious a human cell comprising an exogenous sequence encoding a sialylated protein (e.g. tPA) further comprising a selectable marker (e.g. DHFR) and an exogenous glutamine synthetase sequence wherein these sequences are on more than one DNA vector and the cell is capable of producing the protein and capable of growing in a glutamine-free and serum-free medium (**claim 1**).

Brandt et al teach an HT1080 cell line (see column 8, lines 24-50, for example), which meets the limitation of a glutamine-auxotropic human cell line or an immortalized fibrosarcoma HT1080 cell line (**claims 3-5**).

Brandt et al teach that the cells are cultured in serum-free medium and in suspension (see column 6, lines 25-42, for example). Bebbington et al teach that cells can be transformed to glutamine independence by incorporating a gene encoding GS so that the cells can grow in glutamine-free medium. Therefore, the cells made obvious by Bebbington et al in view of Brandt et al would be capable of growing in suspension in serum-free and glutamine-free medium (**claim 6**).

Brandt et al teach that the cells were cultured to produce the target protein, which was then recovered and quantified from the cell supernatant (see column 6, lines 44-63, for example), which meets the limitation of a process for the production of a sialylated protein in a glutamine-auxotropic human cell in a serum free medium and recovery of the protein (claim 7).

As discussed above, Bebbington et al in view of Brandt et al render obvious a cell capable of growing in serum free and glutamine free medium and would also render obvious a process for producing a sialylated protein by culturing a glutamine-auxotrophic cells wherein the culture medium is serum-free and glutamine free (**claims 10-11).** Brandt et al teach production of a protein such as EPO using an HT1080 cell line (see column 8, lines 24-50, for example), which meets the limitation of a process wherein the cells is a glutamine-auxotropic human cell line or an immortalized fibrosarcoma HT1080 cell line (**claims 19-20 and 25-27**).

In the response filed 4/30/2007, Applicants presented arguments related to 103(a) rejections in the Office action mailed 11/13/2006. See below for response.

Applicants submit that the claimed invention is related to the circumstance where a selectable marker other than GS already had been chosen and was present in cells, but a problem with insufficient sialylation was encountered. Applicants submit that surprisingly supertransfection with a GS marker helped to overcome the sialylation deficiency. Applicants submit that at the time of the GS transfection, all the cloning and clone selection art cited by the Examiner had been accomplished. Applicants submit

that the ordinarily skilled person encountered however the more specific problem of insufficient glycosylation. EPO in particular has been found to have multiple N-glycans and to be highly dependent in its specific activity on sialylation.

Applicants submit that the cited art does not address the problem of sialylation and introducing GS activity into a cell. More specifically, Applicants submit that the ordinarily skill person would not have been motivated by the cited art to have made the claimed invention, such as by combining by way of supertransfection a GS reference with a reference on EPO production by means of DHFR. Applicants submit that the ordinarily skilled artisan may have expected more rapid cloning or clonal selection, however one of ordinary skill would not have expected to have successfully made the claimed invention from the cited art. Applicants submit that the gene amplification with a second selectable marker would not have addressed the problem of enhancing sialylation, and hence specific activity of a glycosylated gene product, as with the claimed invention.

Applicants submit that the cited art is silent with regard to sialylation enhancement using GS. The applicants believe that perhaps the art has failed to appreciate same because proteins previously produced by GS were not dependent in their activity on complete sialylation (i.e., some glycosylation with core glycan was sufficient for activity). Applicants submit that with the use of human cell lines potentially capable of sialylation however, the enhancement of sialylation has become more important. The applicants believe that the CHO cells of Pu et al, for example, do not have a human-like sialylation capacity such that there would not have been incentive in

the art to have combined the cited art with Pu et al to allegedly make the claimed invention. Finally, the applicants note that the medium condition is relevant to the amount of stress placed on cells wherein serum-free conditions have become preferred for avoiding potential disease transmission however these conditions can increase stress.

Response to Arguments

As written, the claims drawn to a glutamine auxotrophic human cell transfected with a DNA sequence encoding a sialylated protein and a process of producing the protein do not require a specific amount of sialylation of the protein or enhanced sialylation. In fact, since some claims are drawn to the cell comprising the gene, it is not necessary for the protein itself to be produced for a reference to be applied to the claimed cell, only that the cell encode a protein that would be sialylated in post translational processing. The claims do not reflect any requirement for supertransfection with a GS marker or enhanced sialylation.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem Mitchell whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like

assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura McGillem Mitchell
Examiner
7/19/2007

CELINE QIAN, PH.D.
PRIMARY EXAMINER